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## Welcome and Opening Remarks Joint Meeting of the Oncologic Drugs and the Pediatric Advisory Committees

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## Purpose of the Meeting

- Discuss the scientific and ethical issues involved in developing drug treatments for children with diffuse intrinsic pontine gliomas (DIPG)
- Among the issues to be considered are:
  - the scientific issues involved in identifying appropriate drug targets to study for the treatment of these tumors and,
  - the ethical issues involved in obtaining and using brain biopsy specimens to evaluate gene expression patterns in children with DIPG.

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## FDA Interest

- The development of standards for microarray and proteomics-based identification of biomarkers and the exploitation of this information to identify appropriate drug targets in cancer therapies are two of the topics included in the March 2006 FDA Critical Path Opportunities List.
- FDA has issued final Guidance on Pharmacogenomic Data Submissions (March 2005) and draft Companion Guidance (August 2007) to facilitate scientific progress in the field of pharmacogenomics and the use of pharmacogenomic data in drug development.

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## Unmet Need

- “In the last 20 years, pediatric neuro-oncology has benefited from a number of advances.”
  - sophisticated neuroradiological and neurosurgical tools, improved radiotherapeutic techniques, new drugs, innovative myeloablative schedules, and specific therapies suited to the molecular profiles of specific tumor subtypes
- “Major progress has been made in survival rates and quality of survival.”
- “These considerations apply to all pediatric CNS tumors except for intrinsic pontine glioma, which remains the grimmest and most frustrating disease pediatric oncologists have to face.”

Massimino et al J Neurooncol (2008) 87:355–361 4

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## Radio- and Chemotherapy for DPG?

- “Overall, radiotherapy induces neurological improvement, allows reduction or discontinuation of steroids, and is associated with radiological response.”
- “Correlation between radiological response and survival has been assessed in only one study, which did not show a survival benefit for radiological responders.”
- “So far no treatment has shown any benefit over conventional radiation. The use of chemotherapy either before or after radiation has not shown any survival advantage. Concomitant chemotherapy and radiotherapy has been investigated in 12 studies and did not seem to confer a survival benefit.”

Hargrave et al Lancet Oncol 2006; 7: 241–48 5

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## The Role of Biological Samples?

- “The genetics of these tumours is complex and includes grade-dependent amplification and overexpression of epidermal growth factor receptor (*EGFR*) and grade-independent expression and mutation of *P53*. With the development of targeted therapies, the issue of stereotactic or open biopsies for diffuse brainstem glioma is being readdressed by some cooperative groups to correlate biological findings with drug activity.”

Hargrave et al Lancet Oncol 2006; 7: 241–48 6

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## Drug Targeting in DPG?

- Finding Drug Targets?
  - “Advances in... imaging technique and... restricted surgical options have led many practitioners to avoid... biopsy procedures and to use MR imaging findings alone for the diagnosis.”
  - “Modern molecular biological diagnostic tools for tumor specimens might justify stereotactic biopsy sampling..., the better to investigate tumor identities for future therapeutic options.”
- But hitting a Target with what Drug?
  - “In light of the lack of evidence for improved outcomes or prolonged survival in patients with diffuse brainstem gliomas, it is difficult to imagine that any of the currently available drugs, even when used in novel combinations, will prove useful in enhancing the dismal outcome of this disease.”

Frazier et al J. Neurosurg - Pediatrics 3:259-269, 2009 7

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## Presentations

- Current Clinical Management (Ken Cohen)
- Science
  - Scientific Proposal – DIPG (Nick Foreman)
  - Challenges in Scientific Design (Lisa McShane)
- Stereotactic Brain Biopsy (Mike Handler)
- Ethics (Steve Joffe)
- Parent Perspective (Loice Swisher)
- Opportunity for Public Comment

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## Some Scientific Considerations

- Samples
  - Is a single biopsy representative of the tumor? How much variation exists within a tumor of one subject? How much variation exists between tumors of different subjects? Can an adequate sample (RNA) be obtained to conduct the necessary studies (i.e., technical replicates for both discovery and validation)? Can one use alternate non-biopsy sources (such as post-mortem specimens, DIPG cell lines)?

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## Some Scientific Considerations

- Class Comparison
  - How many biological replicates are necessary to adequately characterize the class (i.e., number of subjects)? What class should the DIPG samples be compared to? How does one reduce the “false discovery rate” given the large number of observations? How does one interpret the biological meaning (i.e., function) of the observed differences?

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## Some Scientific Considerations

- Drug Targeting
  - Once a class difference is observed, how does one determine that it is a suitable drug target? What strategies must be deployed (e.g., tissue culture, transgenic or knockout animal models) to assess the functional role of the target gene product?

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## Some Ethical Considerations

- Should children be placed at risk for the sake of other children? Should parents be able to permit these risks? Are there limits to these permissible risks? What is the potential impact on the child's quality of life? Is there an obligation to participate in such research? Can a parent make such a decision under the duress of a life-threatening diagnosis?

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## Scientific Question

- Based on your discussion, has the “state of the science” in drug targeting research progressed to where there is a reasonable expectation of success in identifying drug candidates to move into early phase clinical trials for DIPG?
- Please articulate the reasons in support of your answer.

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## Ethical Question

- Assuming a *reasonable expectation of scientific success*, should children with DIPG undergo a non-therapeutic brain biopsy to advance the study of possible drug targets (i.e., for research purposes only)?
- Please articulate the ethical reasons in support of your answer.

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